REMARKS

Status of the Claims

Claims 29, 30, 32-34, 36-43, 45-51, 53-59, 61-68, 70-78, 80-82, 84-86, 91-101, and 103 are pending. Claims 29, 32, 36, 47, 48, 93, 94, 96-98, and 103 have been amended. The amendments to the claims are supported by the specification as originally filed. No new matter has been added. Claims 34, 43, 46, 51, 53-59, 61-68, 70-78, 84-86, 91, and 101 are withdrawn. Claims 41-43, 45, 99, and 100 have been canceled. Upon entry of the present amendment, claims 29, 30, 32, 33, 36-40, 47-50, 80-82, 92-98, and 103 will be pending and under examination.

Rejections under 35 U.S.C. § 103

A. Claims 29, 30, 32, 33, 36-42, 45, 47-50, 92-100, and 103

Claims 29, 30, 32, 33, 36-42, 45, 47-50, 92-100, and 103 were rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 5,658,564 ("Sykes") in view of U.S. Patent No. 6,544,787 ("Slavin"), Nowak, *New Scientist* 19/26:11 (1999) ("Nowak") and U.S. Patent No. 5,434,136 ("Mathias"). Applicant traverses the rejection, in part.

To establish a prima *facie case* of obviousness under 35 U.S.C. § 103(a), the Examiner must: (i) show that the combination of references discloses all the elements of the claim; (ii) advance "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the new invention does . . . " (*KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1731 (2007)); and (iii) show a reasonable likelihood of success. Applicant respectfully submits that the combined references do not render Applicant's claimed invention, for the reasons detailed below.

Amended independent claim 29 is directed to a method for treating an autoimmune disease in a patient having or suffering an autoimmune disease, comprising: depleting T cells in the patient; and reactivating the thymus of the patient, the thymus being reactivated by disruption of sex steroid-

mediated signaling to the thymus, the patient having an improved prognosis for the autoimmune disease compared to an untreated patient suffering from the autoimmune disease.

Amended independent claim 103 is directed to a method for reducing the risk of developing an autoimmune disease in a patient at risk of having or suffering an autoimmune disease, comprising: depleting T cells in the patient; and reactivating the thymus of the patient, the thymus being reactivated by disruption of sex steroid-mediated signaling to the thymus, the patient having a reduced risk of developing the autoimmune disease compared to an untreated patient at risk of having, or suffering from, the autoimmune disease.

Applicant respectfully submits that the Office Action has not set forth a *prima facie* case of obviousness because the Office Action: (i) fails to show that the combination of references discloses all the elements of Applicant's claims; (ii) fails to provide a motivation to modify the primary reference with the secondary references; and (iii) fails to show a reasonable likelihood of success.

Sykes

The primary reference used as the basis for the rejection in the Office Action is Sykes. According to the Office Action, at pages 3-4 (emphasis added):

> Sykes et al disclose at least a method of restoring or inducing immunocompetence or restoring or promoting the thymus-dependent ability for T cell progenitors to mature or develop into functional mature T cells in a host or recipient, including a human adult or a human child, said method comprises the steps of introducing into said host donor thymic tissue....Please be noted that a recipient receiving donor thymic tissue, particularly fetal or neonatal thymic tissue, falls within the scope of a patient with a thymus undergoing reactivation.

The Office Action also states, at page 10, that:

> After the implantation, the donor thymus belongs to the treated patient in the method taught by the Sykes reference and it is a body part of

> the treated patient, and therefore it is within the broad scope of "the thymus of the patient."

Applicant respectfully disagrees.

Sykes describes a method for replacing thymus function and introducing and restoring immunocompetence (or restoring or promoting the thymus-dependent ability of T cell progenitors to mature or develop into functional mature T cells) in a recipient. The recipient to be treated is capable of producing T cell progenitors but is unable to produce a sufficient number of mature functional T cells for a normal immune response (*see* col. 1, lines 37-45). In Sykes' method, donor thymic tissue is introduced into a recipient so that recipient T cells can mature in the implanted donor thymic tissue (*see* col. 1, lines 45-49).

In contrast to Sykes, the pending claims relate to reactivating the thymus of a patient. One of ordinary skill in the art would not consider the claims, which recite "reactivating the thymus of the patient," as meaning reactivating a donor thymus transplanted into the patient, as described by Sykes. When tissue is transplanted into a patient, the field of immunology recognizes that the donor tissue is not "of the patient." In fact, one of the challenges in transplanting donor tissue into a recipient is the very fact that the recipient's immune system recognizes the donor tissue as "*foreign*" and not "of self." Accordingly, one of ordinary skill in the art reading "thymus of the patient" would not consider this to include a donor thymic tissue transplanted into the patient.

Further, after transplanting a thymus into a patient, as described by Sykes, one of ordinary skill in the art would not consider the need to reactivate the transplanted thymus. The specific donor thymic tissue described by Sykes is fetal or neonatal, and, as such, the donor thymic tissue is already *activated*. There would be no need to reactivate Sykes' transplanted thymus, as recited in the claims. Thus, even if a transplanted thymus could be considered to be a "thymus of the patient" (which Applicant does not concede), one of ordinary skill in the art would not be led to a method of treating an autoimmune disease by reactivating the thymus *of the patient* (whether native or transplanted).

In addition, the pending claims recite methods of treating, or reducing the risk of developing, an autoimmune disease. Reading Sykes, one of ordinary skill in the art would not be led to a method for treating an autoimmune disease in a patient at all. As discussed above, Sykes is concerned with treating patients who are unable to produce a sufficient number of mature functional T cells for *a normal* immune response (*see* col. 1, lines 37-45).

Autoimmune diseases are not characterized by an inability to produce sufficient numbers of mature functional T cells for a normal immune response. In contrast, autoimmune diseases are characterized by an *aberrant* immune response directed against self, and may be mediated, for example, by a cohort of autoreactive T cells in the periphery.

Accordingly, as Sykes says nothing about treating autoimmune disease, and Sykes addresses problems that are different from those underlying autoimmune disease, one of ordinary skill in the art would not be led to any treatment of autoimmune disease. In fact, increasing the number of mature T cells as described in the treatment methods of Sykes may well exacerbate an autoimmune disease, particularly if it is mediated by autoreactive T cells.

Moreover, the types of diseases described by Sykes are fundamentally different from autoimmune disease. Sykes describes methods of restoring or inducing immunocompetence in a recipient at risk for an acquired immune disorder defined as being due primarily to other than genetic defects (*see* col. 5, lines 29-40; col. 7, lines 21-29; and col. 9, lines 8-20). Examples of acquired immune disorders include AIDS and immunocompetence resulting from neoplastic disease or from a medical procedure such as chemotherapy or radiation treatment (*see* col. 15, lines 28-38). The methods described by Sykes involve the introduction of donor thymic tissue and/or donor hematopoietic stem cells into a recipient. Whether donor thymic tissue and/or hematopoietic cells are used depends on whether the recipient's thymus is capable of supporting the maturation of T cells (in terms of number and/or immune responsiveness) as compared with a normal individual (*see* col. 14, lines 60-65; and col. 14, lines 31-44) and/or whether the recipient is capable of producing T cell progenitors.

These methods are not at all relevant to the treatment of autoimmune disease. First, one of ordinary skill in the art would not consider an autoimmune disease as a type of acquired immune disorder, as autoimmune diseases typically have a genetic basis. In addition, as stated above, autoimmune diseases are not characterized by an inability to produce sufficient numbers of mature functional T cells for a normal immune response. Finally, autoimmune diseases are not characterized by an inability to produce T cell progenitors. Thus, Sykes' treatment of acquired immune disorders says nothing about the treatment of autoimmune disease.

Furthermore, one of ordinary skill in the art, reading Sykes, would conclude that a patient's thymus should be removed rather than reactivated. Sykes describes methods to confer tolerance to both allogeneic grafts and xenogeneic grafts (*see* col. 17, lines 1-6) that rely on introducing donor thymic tissue into a recipient. Sykes insists that the donor of the graft and the donor that supplies the tolerance-inducing thymic tissue should be the same or as closely related as possible (*see* col. 17, lines 7-9). The studies described by Sykes demonstrate that mature murine T cells in athymic C57BL/10 (B10) mice but not in euthymic B10 mice that received fetal swine thymus/liver transplants (following treatment with depleting doses of anti-T cell and anti-NK cell mAbs and mediastinal and whole body irradiation) were tolerant to swine antigens (*see* col. 17, lines 50-53). Sykes reasons that tolerance to swine antigens is not induced in the euthymic mice that received thymus/liver grafts (thereby causing the swine thymus/liver grafts to be rejected) because murine T cell progenitors matured in the host thymus, which lacks the swine cells necessary to tolerize developing murine thymocytes (*see* col. 19, lines 22-26). Accordingly, Sykes concludes that if the recipient has significant thymic function, thymectomy is indicated (*see* col. 21, lines 18 and 19). As such, Sykes teaches away from methods involving reactivating a patient's thymus. Indeed, Sykes makes it clear that a patient's thymus should be removed, not reactivated.

Additionally, it is clear that Sykes describes methods that all include the use of donor thymic tissue. The Office Action wrongly opines that Sykes describes methods of treating a mammal, including a human adult or a human child, who does not necessarily have a thymus transplanted into the mammal (at p. 10, lines 11-22). However, Sykes does not teach such methods.

Sykes presents data that fetal swine livers grafted without donor thymic tissue did not grow in control mAb-treated thymectomised B10 mice that received 108 fetal swine liver cells i.p. (*see* col. 17, lines 14-30; col. 17, lines 58-62; col. 19, lines 31-36; and col. 20, lines 20-23). In other words, swine hematopoietic stem cells present in the fetal liver cell suspension failed to induce tolerance to the grafted liver, resulting in graft rejection. Sykes describes that tolerance to swine antigens was induced following swine thymus/liver transplants. Further, Sykes shows that a significant degree of chimerism was not detected in a sublethally irradiated SCID mouse implanted with a swine fetal liver under the kidney capsule *without donor thymic tissue*. Sykes also demonstrates that in mice receiving swine fetal thymus/liver grafts, 25-50% of the peripheral blood leukocytes were of donor lineage two weeks post transplantation (*see* col. 27, lines 5-11). According to Sykes, the formation of chimeric bone marrow promotes long-term survival of the graft through T-cell and B-cell mediated tolerance (*see* col. 26, lines 32-35). Finally, Sykes concedes that a kidney implanted in cynomolgus monkey following liver absorption of natural antibodies, administration of anti-thymocyte globulin, sublethal irradiation, and bone marrow infusion was rejected 7 days post-transplant (*see* col. 26, line 60, to col. 27, line 4). Again, these results highlight the importance of providing the recipient with donor thymic tissue to induce tolerance to the graft. Based on these teachings, one of ordinary skill in the art, reading Sykes, would appreciate that the methods described by Sykes require donor thymic tissue to induce tolerance to the graft and prevent it from being rejected.

The Office Action's characterization of Sykes (*i.e.*, of "reactivating" the patient's thymus instead of providing donor thymic tissue) is contrary to the principle of operation taught by Sykes for inducing tolerance, thereby rendering the methods disclosed by Sykes unsatisfactory for their intended purpose. That is, reactivation of the recipient's thymus fails to provide the donor thymic tissue necessary to tolerize developing recipient thymocytes to donor antigens, which, according to Sykes, would lead to rejection of the donor graft.

Thus, taken as a whole, Sykes describes methods of treating acquired immune disorders by transplanting already activated donor thymus into a patient, and accordingly, one of ordinary skill in

the art would not be led to methods of reactivating a patient's own thymus to treat autoimmune diseases.

Mathias

The Office Action relies on Mathias to modify the teachings of Sykes to extend to the treatment of autoimmune diseases. Applicant respectfully disagrees that Mathias would lead to treatment of autoimmune diseases.

According to the Office Action (at pages 11-12, emphasis in original):

> with respect to the Mathias reference it is noted that **treating motility disorders which are secondary disorders associated with autoimmune disorders** falls within a broad scope of "treating or alleviating symptoms of an autoimmune disease" in a patient of the methods as claimed. Nevertheless, Mathias stated "The present invention relates to the treatment of functional motility disorders including diseases of the autonomic nervous system of idiopathic or known causes. **Treatment of Functional Bowel Disease or disease of the irritable bowel, as well as the autonomic dysfunction of autoimmune diseases such as Systemic Lupus Erythematosus (SLE) with an analog of GnRH is disclosed**." Any reasonable person would clearly understand that Mathias teaches a treatment method at least for SLE, an autoimmune disease, using an analog of GnRH.

Applicant respectfully disagrees.

Mathias describes methods of treating motility disorders (including diseases of the autonomic nervous system of idiopathic or known causes) which are associated with autoimmune diseases such as Systemic Lupus Erythematosus (SLE) and not to autoimmune diseases *per se* (*see* col. 2, lines 44-47; and col. 2, line 62, to col. 3, line 10). One of ordinary skill in the art would understand that Mathias describes the treatment of autonomic dysfunction of autoimmune diseases (*i.e.*, a secondary disorder associated with autoimmune diseases such as SLE) and not the autoimmune disease itself.

Applicant has amended claim 29 to recite the treatment of an autoimmune disease *per se*, making it even more clear that Mathias does not render the pending claims obvious. Indeed, it is unclear from the Office Action how a possible benefit on a secondary disorder would lead one of ordinary skill in the art to methods of treating an autoimmune disease or reducing the risk of developing an autoimmune disease, as presently claimed.

Slavin

The Office Action cites Slavin as an additional secondary reference that allegedly leads to modifying the teachings of Sykes to the treatment of autoimmune diseases.

According to the Office Action (at page 11, emphasis in original):

> the Slavin reference teaches clearly **a method for treating a human patient with an autoimmune disease comprising the step of transplanting a donor-derived preparation that includes allogeneic stem cells that are obtained from bone marrow, mobilized peripheral blood or cord blood**. Therefore, this teaching is relevant to the teachings of the primary Sykes reference, and it is one of the threads to combine the cited references **to render the instant broadly claimed invention as a whole was *prima facie* obvious**.

Applicant respectfully disagrees that Slavin would lead one of ordinary skill in the art to the claimed methods.

Slavin describes the administration of a sub-myeloablative/lymphoablative (m/L) or lymphoablative (-/L) conditioning regimen (which eliminates a patient's T cells while allowing retention of a functional population of the patient's hematopoietic stem cells) followed by transplantation of a donor-derived allogeneic stem cell preparation (*see* col. 2, lines 38 47). According to Slavin, patients treated by this method develop donor-specific unresponsiveness (resulting in acceptance of the allogeneic stem cell graft) and develop fewer complications when compared to standard myeloablative/lymphoablative (M/L) regimens (which involves the

elimination of substantially all the hematopoietic stem cells and lymphocytes of the patient) (*see* col. 2, lines 31-34). Slavin suggests that allogeneic stem cell transplantation leading to engraftment of allogeneic stem cells in the host may function merely to induce a state of host-versus-graft tolerance, providing a platform for performing allo-cell therapy for inducing graft versus leukaemia, graft versus tumour and graft versus autoimmunity effects (*see* col. 2, lines 5-11; and col. 2, lines 34-36).

Based on Slavin, one of ordinary skill in the art would not be led to methods of treating an autoimmune disease in a patient by reactivating the patient's thymus. Rather, Slavin describes methods that include "allo-cell therapy approaches following relatively safe stem cell *transplants* using the disclosed conditioning regimens" (col. 12, lines 34-37). In other words, Slavin describes the treatment of an autoimmune disease by induction of graft versus autoimmunity (analogous to graft versus tumour) effects mediated by alloreactive donor lymphocytes. This is in contrast to the methods of the claims, which involve the ablation of an aberrant or "self-reactive" immune system and reactivation of the thymus to facilitate regeneration of a new self tolerant immune system from hematopoietic cells.

Nowak

Nowak teaches that blocking sex hormones may mediate regeneration of the immune systems of people with HIV or who have had chemotherapy or bone marrow transplants, by reactivating the thymus. Nowak is silent as to reactivation of a patient's thymus for the treatment of an autoimmune disease. This is not surprising, given that a boost in the immune system of a patient suffering from an autoimmune disease is likely to *exacerbate* the characterizing aberrant immune response against self. Thus, one of ordinary skill in the art would not consider the methods described by Nowak to be applicable to methods of treating a patient having an autoimmune disease.

Further, the methods described by Slavin result in immunosuppression, which is directly opposed to the methods described by Nowak, which result in boosting the immune system. In this

regard, one of ordinary skill in the art would not consider combining the methods described by Nowak with the methods described by Slavin. Indeed, the Office Action's attempt to combine the teachings of Nowak and Slavin is seemingly an attempt to arrive at the pending claims based on impermissible hindsight gleaned only from the Applicant's disclosure.

For the reasons discussed above, Sykes, Slavin, Nowak, and Mathias, whether alone or in combination, would not lead one of ordinary skill in the art to Applicant's pending claims 29, 30, 32, 33, 36-40, 47-50, 92-98, and 103. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this 35 U.S.C. § 103(a) rejection.

B. Claims 80-82

Claims 80 and 81 were rejected under 35 U.S.C. § 103(a) as unpatentable over Sykes in view of Slavin, Nowak, and Mathias, and further in view of Bolotin *et al.*, *Blood* 88:1887-1894 (1996) ("Bolotin"). Claims 80 and 82 were rejected under 35 U.S.C. § 103(a) as unpatentable over Sykes in view of Slavin, Nowak, and Mathias, and further in view of Tian *et al.*, *Stem Cells* 16:193-199 (1998) ("Tian"). Applicant respectfully traverses these rejections.

Claim 80 depends from claim 29 (which recites a method for treating an autoimmune disease in a patient having or suffering an autoimmune disease), and further comprises administering a cytokine, a growth factor, or a combination of a cytokine and a growth factor to the patient. Claim 81 depends from claim 80, and recites that the cytokine is selected from the group consisting of Interleukin 2 (IL-2), Interleukin 7 (IL-7), Interleukin 15 (IL-15), and combinations thereof. Dependent claim 82 is based on claim 80, and recites that the growth factor is selected from the group consisting of a member of the epithelial growth factor family, a member of the fibroblast growth factor family, stem cell factor, granulocyte colony stimulating factor (G-CSF), keratinocyte growth factor (KGF), insulin-like growth factor, a growth hormone, a thyroid hormone, and combinations thereof.

As discussed above, the combination of Sykes, Slavin, Nowak, and Mathias fails to render claim 29 obvious, and, as neither Bolotin nor Tian cures this deficiency, dependent claims 80-82 are not obvious over these references.

Although Bolotin does teach IL-7, Bolotin discloses the use of IL-7 to promote thymic reconstitution and enhance thympoiesis after bone marrow transplantation (BMT) to prevent post-BMT immune deficiency. However, Bolotin does not teach or suggest the use of IL-7 to treat an autoimmune disease in a patient having or suffering an autoimmune disease as presently claimed.

Tian teaches that recombinant human growth hormone promotes hematopoietic reconstitution after syngeneic BMT and may be useful to accelerate hematopoiesis after autologous BMT. However, Tian does not teach or suggest the use of a growth factor in methods for treating an autoimmune disease in a patient having or suffering an autoimmune disease.

One of ordinary skill in the art would not consider Bolotin or Tian to be applicable in methods of treating autoimmune disease in patients. Accordingly, claims 80 and 81 are not obvious over the cited references, and Applicant respectfully requests reconsideration and withdrawal of this 35 U.S.C. § 103(a) rejection.

Double Patenting

Claims 29, 30, 32, 33, 36, 37, 39-42, 45, 47-50, 80-82, 92, 94-100, and 103 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 19, 20, 23, 25, 28-31, 34-36, 38-40, 55, 57-60, 62, 64, 66, and 68 of copending Application Serial No. 10/749,119.

Applicant respectfully requests that this rejection be held in abeyance until such time as the claims are in condition for allowance. At such time, if necessary, Applicant will file a Terminal Disclaimer.

CONCLUSION

Applicant submits that the pending claims are in condition for allowance and reconsideration of the rejections and allowance are respectfully requested.

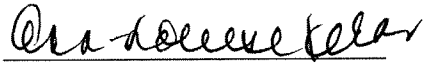
Applicant is filing concurrently a Request for Continued Examination and a Petition for Extension of Time for three months, extending the deadline for filing a response up to, and including, March 10, 2009.

Please charge any fees or apply any overages to our Deposit Account No. 08-0219 under our order number 0286336.151US1 / NOR-012CP2, from which the undersigned is authorized to draw.

The Examiner is encouraged to call the undersigned to facilitate prosecution of this case.

Respectfully submitted,

Dated: March 10, 2009



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